Lymphocytic Thrombophilic Arteritis Induced by Minocycline

[a]MICHAEL KASSARDJIAN, DO; [a]DAVID HOROWITZ, DO, FAOCD, FAAD;
[b]PAUL K. SHITABATA, MD; [c]LANI E. CLARK, MD, FAAD

[a]Department of Dermatology, Western University of Health Sciences/Pacific Hospital of Long Beach, Long Beach, California;
[b]Dermatopathology, Harbor-UCLA Dermatology, Torrance, California; [c]Dermatologist, Private Practice, Los Alamitos, California

ABSTRACT

Lymphocytic thrombophilic arteritis is an entity only recently defined in the literature. This term describes a distinctive histopathological combination of lymphocytic vascular inflammation associated with a hyalinized fibrin ring in the vessel lumina, changes reflecting a thrombophilic endovasculitis. The authors present the case of a woman who developed lymphocytic thrombophilic arteritis coinciding with the use of minocycline. In addition to these histopathological findings, the cutaneous manifestations of this case reflect previously reported clinical findings of progressive localized livedo racemosa characterized by reticular patchy hyperpigmentation predominately affecting the lower extremities.
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Lymphocytic thrombophilic arteritis (LTA) is an entity only recently described in the literature. This term was used to describe the distinctive histopathological combination of lymphocytic vascular inflammation with thrombophilic endovasculitis. Lee et al[1] reported five cases of LTA that demonstrated the histopathological finding of lymphocytic vasculitis that was associated with a hyalinized fibrin ring in the vessel lumina. Clinically, patients presented with a progressive localized livedo racemosa characterized by reticular patchy hyperpigmentation predominately affecting the lower extremities. Generally, lesions were asymptomatic without ulceration or purpura. Additionally, all reported cases in the literature describe young women ranging from 20 to 34 years of age.[1,2] Although lesions are typically asymptomatic, they are cosmetically concerning to patients and often are the reason medical management is sought.

CASE REPORT

The authors present the case of a 40-year-old, healthy, Caucasian woman who developed asymptomatic, smooth, brownish-red blanching reticulated patches on her lower extremities bilaterally. The patient reported no systemic symptoms and denied any extremity pain. However, these cutaneous findings were cosmetically displeasing to the patient. Minocycline, prescribed for acne, was the only medication started three months prior. Over the next three months, despite topical steroid treatment, the rash progressed to involve primarily the anterior forearms with a slight rash on the posterior forearms and upper arm, sparing the trunk and face in a livedo racemosa pattern (Figure 1). At this point, labs were ordered, including antinuclear antibody (ANA) panel, lupus anticoagulant, cardiolipin antibody, C-reactive protein (CRP), rapid plasma reagin (RPR), hepatitis panel, parvovirus B-19, and urinalysis. Positives included a nucleolar ANA at 1:160, weak positive histone antibodies at 1.2, weak positive lupus anticoagulant in the hexagonal phase, and partial thromboplastin time (PTT) at 42 (<40). A skin biopsy was then performed (Figure 2) and sent for hematoxylin and eosin and direct immunofluorescence, which was negative. Minocycline was stopped, which coincided with a halt of progression of skin lesions, leaving postinflammatory hyperpigmentation. Following cessation of the medication, the patient's lesions slowly resolved without any additional intervention over the ensuing months. Lab results revealed a reduction in the ANA titer (1:80), a similar lupus anticoagulant, and a minor decrease in antihistone antibodies to 1.1.

Histopathology revealed an unremarkable epidermis. Situated within the deep reticular dermis, at the junction of the subcutaneous adipose tissue, is a medium-sized vessel

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ADDRESS CORRESPONDENCE TO: Michael Kassardjian, 23550 Hawthorne Blvd. #200, Torrance, CA 90505; E-mail: kassardjian@coastdermatology.com

with prominent fibrinoid necrosis involving the wall, forming a concentric ring. An elastic fiber stain showed focal disruption within the wall of the vessel. The vessel wall is infiltrated by mature lymphocytes and rare plasma cells (Figure 3).

DISCUSSION

The authors present the first case of a newly termed entity, *lymphocytic thrombophilic arteritis*, which coincides with the use of minocycline. Although the anticardiolipin antibody was negative, there was positive lupus anticoagulant antibody reactivity. The elevated antihistone antibody suggests a drug-induced lupus phenomenon; however, its significance is uncertain due to such a low elevation. The histopathology mirrors cases previously reported with a distinct histopathological combination of a lymphocytic vasculitis associated with a hyalinized fibrin ring in the vessel lumina, changes reflecting a thrombophilic endovasculitis. In addition, the authors demonstrate a similar cutaneous manifestation. The mechanism of minocycline involvement in this entity is uncertain and warrants more investigation.

LTA is a condition recently described in the literature with few reported cases. Lee et al[1] described LTA in five women—one Chinese, one biracial (Japanese-English), one Indian, and two Middle-Eastern—who had livedo racemosa, reticular hyperpigmentation, and on histopathological analysis, an infiltration of the arterioles walls with lymphocytes coupled with rings of fibrin in the vessel walls.[1] Lymphocytic vasculitis is a rare finding and is defined as a lymphocytic inflammation of the small vessels in the upper dermis with resultant vessel damage and hemorrhage. This term is used to implicate lymphocytes are the primary source of damage to the vessel walls.[3] Ackerman and Mones[4] further describe lymphocytic vasculitis as infiltration of lymphocytes usually perivascularly, both superficial and deep, with fibrin in the wall or thrombi within the lumen of venules.[4]

In cases of LTA, lymphocytes are unlikely to be a secondary reaction to fibrin deposition in vessel walls, but have the ability to injure the endothelial cells of arteriole walls. Therefore, there is a possibility for endothelial cells to be the primary target for lymphocytes.[5] Although muscle vessel wall infiltration by lymphocytes and histiocytes with intraluminal fibrin deposition is a form of medium-sized vessel lymphocytic vasculitis, LTA could not be classified into the known categories for vasculitis based on the Chapel Hill Consensus Conference criteria and the American College of Rheumatology criteria.[1,6,7] Additionally, Lee et al[1] noted that the presence of the hyalinized fibrin ring intramurally reflected a thrombophilic state, possibly indicating a focal thrombophilia stimulated by lymphocytic endovasculitis, which histopathologically differentiates this entity.

Lymphocytes also have the potential of stimulating extravascular and chronic inflammation, as well as activation of Langerhans cells.[8] Additionally, lymphocytes have been reported to have the capability to stimulate

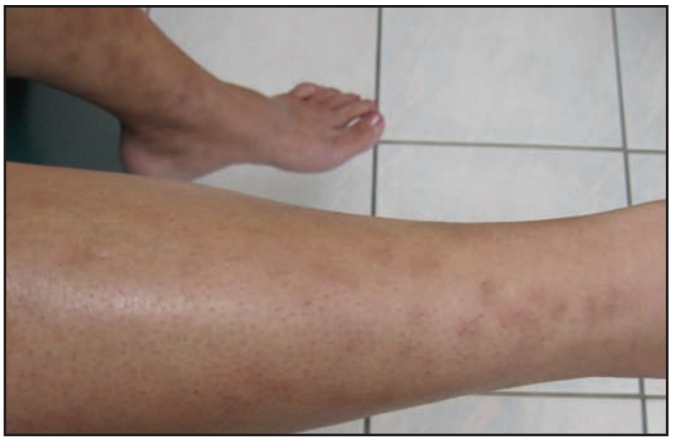

Figure 1. Smooth brownish-red blanching reticulated patches on lower extremities that progressed to involve upper extremities, sparing the trunk

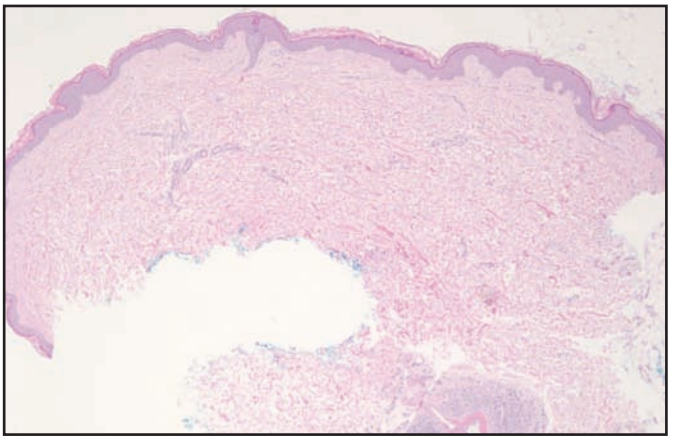

Figure 2. Medium-sized vessel with prominent fibrinoid necrosis involving the wall, forming a concentric ring located in the deep dermis

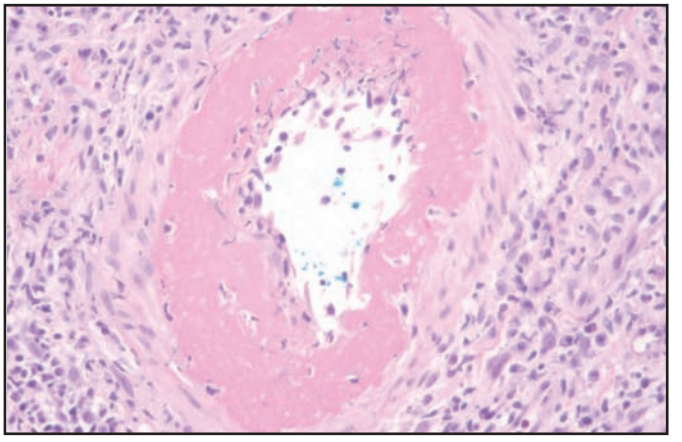

Figure 3. 40x magnification showing prominent fibrinoid necrosis involving the wall, forming a concentric ring with infiltration of lymph

TABLE 1. Clinical and histological features of macular arteritis, cutaneous polyarteritis nodosa, and lymphocytic thrombophilic arteritis

	MACULAR ARTERITIS	CUTANEOUS POLYARTERITIS NODOSA	LYMPHOCYTIC THROMBOPHILIC ARTERITIS
CLINICAL FEATURES	• Hyperpigmented, reticular patches and macules • Typically affects lower extremities • Characteristically asymptomatic • Range in size from 0.5 to 3.5cm	• Characteristically livedo reticularis • Severe digital ischemia may occur with accompanying splinter hemorrhages and gangrene • Painful nodules typically on the lower extremities • Possible ulcerations especially on the lower extremities near malleoli and on the calf • Systemic multiorgan symptoms may result	• Typically progressive localized livedo racemosa characterized by reticular patchy hyperpigmentation • Predominately affects the lower extremities • Generally, lesions are asymptomatic without ulceration or purpura
HISTOLOGICAL FEATURES	• Lymphocytic infiltration in the muscular wall of small arteries • Hyalinized fibrin ring in the vessel lumen • Associated fibrinoid necrosis • Intimal proliferation with subsequent endarteritis obliterans	• Fibrinoid necrosis in medium-sized muscular arteries secondary to initial intimal inflammation later extending to fully involve the arterial wall • Predominately occurs at bifurcations and branch points. • Focal necrotizing arteritis with mixed cellular infiltrates in the vessel wall • Early stage reveals neutrophilic infiltration with fibrinoid necrosis involving medium-sized arteries • Later stages of PAN predominately show mononuclear cell involvement and fibrosis • Subacute stage of CPAN demonstrates an intimal fibrin ring deposition • Reparative stage exhibits a residual intimal ring in assocation with occlusion of the vessel lumen by a myxoid fibro-intimal proliferation	• Deep reticular dermis at the junction of the subcutaneous adipose tissue. • Distinct histopathologic combination of a lymphocytic vasculitis with prominent fibrinoid necrosis • Forms a concentric ring and mature lymphocytes infiltrating the vessel lumen with rare plasma cells. • Exhibits a hyalinized fibrin ring in the vessel lumina, with changes reflecting a thrombophilic endovasculitis

endothelial surfaces to become a procoagulant as well as induce vessel wall changes leading to alteration of intravascular fibrin deposition, coagulation, and initiation of intimal hyperplasia.[5] Four of the reported cases by Lee et al[1] had positive antiphospholipid antibodies, but due to their transient and low levels of these antibodies in some cases and the absence of other manifestations of vessel occlusion elsewhere, these patients did not meet the criteria for antiphospholipid syndrome. Although their role is unclear, it was unlikely that antiphospholipid antibodies was the cause of LTA.[1,9] Antiphospholipid syndrome is an autoimmune entity with the clinical features of antiphospholipid antibodies first described in 1983 with characteristics that included tendency of thrombosis both arterial and venous, recurrent abortions, and occasional thrombocytopenia, which was later named antiphospholipid syndrome.[10,11] Furthermore, unlike LTA, antiphospholipid syndrome histologically demonstrates vascular thrombosis without significant vessel wall inflammation.[12] In contrast, LTA demonstrates intense mononuclear infiltrate within the deep dermal arterioles, further differentiating it from antiphospholipid syndrome-associated vasculopathies.[1]

Livedo reticularis is the most commonly observed dermatological lesion in antiphospholipid syndrome.[13] Livedo reticularis is described as a violaceous macular erythematous net-like pattern observed cutaneously.[14] In 1907, a second form of livedo was differentiated and termed livedo racemosa, which, similar to its counterpart, cutaneously demonstrates violaceous net-like patterns.[15] However, unlike livedo reticularis, which predominately occurs on the lower extremities, livedo racemosa may present more generally, occurring on the trunk and buttocks in addition to the extremities. Furthermore, livedo racemosa typically presents as irregular broken circular segments, while livedo reticularis consists of regular unbroken circular segments with livid rings in both entities presenting secondary to decreased blood flow at the peripheral skin segments.[16,17] There has been a reported association between livedo racemosa with cerebral ischemic events, seizures, hypertension, and Raynaud's phenomenon.[13] Furthermore, livedo racemosa has also been described as the typical sign of Sneddon's syndrome.[18] A statistically significant higher prevalence of livedo reticularis in antiphospholipid syndrome patients with arterial thrombosis has also been reported, possibly suggestive of endothelial cells function in this cutaneous manifestation.[13,19] All five reported cases of LTA by Lee et al[1] described the clinical presentation of fixed livedo racemosa over the lower extremities and to a lesser extent over the upper extremities in four of the patients. Similarly, the case described here demonstrated asymptomatic brownish-erythematous blanching reticulated patches on the lower extremities bilaterally, which progressed more generally to involve the anterior and slightly the posterior aspects of the forearms in a livedo racemosa pattern.

Macular arteritis is a recently described cutaneous arteritis presenting with hyperpigmented macules that according to Lee et al[1] has a vasculitic process identical to the cases of LTA. Fein et al[20] coined the term macular arteritis in 2003, describing three African American patients presenting with hyperpigmented macules on the lower extremities in a relative uniform pattern, which revealed a lymphocyte-mediated arteritis in the superficial subcutaneous fat and the absence of neutrophils histologically.[20] Clinically, macular arteritis presents with hyperpigmented, reticular patches and macules that favor the lower extremities, with lymphocytic infiltration in the muscular wall of small arteries with a hyalinized fibrin ring in the vessel lumen.[20,21] None of the cases reported had livedo racemosa. Macular arteritis predominantly affects females, with 50 percent of reported cases affecting African Americans. It presents as asymptomatic lesions, predominantly round to oval, that are confluent hyperpigmented macules ranging from 0.5 to 3.5cm.[22] The etiology of macular arteritis is unknown, although of the reported cases, two patients were weakly positive for anticardiolipin antibodies, while others were positive for ANA and anti-SS-A antibodies. None of these cases demonstrated systemic connective tissue disease. Furthermore, low titers of these antibodies may be seen in healthy individuals.[22,23] Therefore, similar to previous reports of LTA, it is unlikely that macular arteritis is a result of these antibodies. Similarly, the authors' case histologically demonstrates a medium-sized vessel with prominent fibrinoid necrosis forming a concentric ring within the deep reticular dermis and mature lymphocytes infiltrating the vessel lumen with rare plasma cells. However, this case of LTA demonstrates these histological findings with a recognizable clinical livedo racemosa, differentiating it from the hyperpigmented macular presentation of macular arteritis. As previously described by Gupta et al,[2] the similar histological findings of LTA and macular arteritis may represent the same disease entity, but have clinically manifested differently as hyperpigmented macules as opposed to a reticulate livedo racemosa, and the term lymphocytic thrombophilic arteritis may better encompass these entities.[2]

Polyarteritis nodosa is another form of vasculitis primarily affecting the medium- and small-sized arteries. Polyarteritis nodosa (PAN) may involve multiorgan systems with systemic symptoms or may be limited solely cutaneously.[24,25] Kussmaul and Maier first described PAN in 1866 after an autopsy of a patient with fever, weight loss, abdominal pain, and polyneuropathy revealed palpable nodules following medium-sized arteries with localized inflammatory exudations.[26] Fibrinoid necrosis arises in medium-sized muscular arteries secondary to initial intimal inflammation that later extends to fully involve the arterial wall, predominately occurring at bifurcations and branch points.[27] Subsequently, obstruction and ultimately tissue ischemia or infarction may result. The American College of Rheumatology developed classification criteria for vasculitides in 1990, which defined the diagnosis of PAN when three of the following 10 criteria are present: weight loss of 4kg or more, livedo reticularis, testicular pain or tenderness, myalgia or leg weakness, mononeuropathy or polyneuropathy, diastolic blood pressure greater than

90mm/Hg, elevated blood urea nitrogen and creatinine levels, infection with hepatitis B virus, abnormal arteriography, and biopsy of small- or medium-sized artery that consists of polymorphonuclear neutrophils.[24] However, this criterion does not include a comprehensive classification system that combines both histopathological and clinical criteria. Therefore, LTA may fit components of both the American College of Rheumatology and the Chapel Hill Consensus Conference criteria, but neither completely defines this entity.[6] Although the pathogenesis of PAN is unknown, when associated with viral infections, such as hepatitis B, previous studies have demonstrated immune complex-induced disease.[27]

Polyarteritis nodosa characteristically presents with cutaneous manifestations of livedo reticularis, severe digital ischemia that may be accompanied by splinter hemorrhages and sometimes gangrene, painful nodules typically on the lower extremities, and ulcerations especially on the lower extremities near the malleoli and on the calf.[25,27] Clinically, reported cases of LTA differ from PAN due to the absence of purpura or ulceration, and unlike painful lesions associated with PAN, cutaneous findings in LTA are predominately asymptomatic.[1] Minocylcine has been well documented in previous case reports as a cause of cutaneous polyarteritis nodosa.[28–32] Histological findings of PAN demonstrate focal necrotizing arteritis with mixed cellular infiltrates in the vessel wall. Early-stage polyarteritis nodosa reveals neutrophilic infiltration with fibrinoid necrosis involving medium-sized arteries, while later stages of PAN predominately show mononuclear cell involvement and fibrosis.[33] The second subacute stage of cutaneous polyarteritis nodosa (CPAN) histologically demonstrates an intimal fibrin ring deposition. Stage 3, the reparative stage, exhibits a residual intimal ring in association with occlusion of the vessel lumen by a myxoid fibrointimal proliferation.[34] Nerve biopsy characteristically exhibits axonal degeneration and fiber loss with segmental demyelination.[35] Lymphocytic thrombophilic arteritis histopathologically has similarities to stages 2 and 3 in cutaneous polyarteritis nodosa and demonstrates infiltration of lymphocytes and histiocytes within the muscular walls and absent or minimal neutrophils. LTA also exhibits hyalinized fibrin ring within the vessel lumina, which is characteristic of reported cases of lymphocytic thrombophilic arteritis.[1] Previous cases have demonstrated considerable overlap between macular arteritis and CPAN, suggestive of a continuum between these diagnoses.[36] Additionally, LTA may represent a latent form of cutaneous polyarteritis nodosa, as many lesions of CPAN heal with violaceous livedoid or hyperpigmented and retiform lesions, persisting for months to years.[37]

A definitive form of treatment has not been described for LTA. Lee et al[1] reported one case that responded to oral prednisolone therapy, but following tapering of the medication, the patient's lesions reappeared. Furthermore, patients did not respond to clopidogrel in combination with aspirin, nifedipine in combination with aspirin, or exclusive aspirin therapy.[1] Similarly, Uthman et al[19] reported that no treatment has proven effective for the management of livedo racemosa, including anticoagulant and antiplatelet therapy.

LTA is an entity only recently described in the literature, which may represent a fascinating intermediate stage and continuum of other vasculitides. The clinical manifestations of LTA demonstrating livedo racemosa may overlap with other more serious vasculitides, especially CPAN, and complete workup should be done to rule out these entities. LTA may represent a form of latent CPAN, as CPAN is denoted by muscular vessel vasculitis and resolves with a retiform hyperpigmentation. Furthermore, the histopathological similarities of LTA with macular arteritis may truly represent the same disease state, but with a different cutaneous manifestation. The term lymphocytic thrombophilic arteritis defines a distinctive pattern of lymphocytic endarteritis, which may be in the setting of macular arteritis. The authors present the first case of LTA that coincides with the use of minocycline, expanding the clinical-pathological spectrum. LTA describes the distinctive histopathological combination of lymphocytic vascular inflammation with thrombophilic endovasculitis associated with a hyalinized fibrin ring in the vessel lumina. In addition to these histopathological findings, this case reflects the clinical findings of patients with a progressive localized livedo racemosa characterized by reticular patchy hyperpigmentation predominately affecting the lower extremities.

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